HIV/TB Coinfection: Case Management and Treatment Challenges

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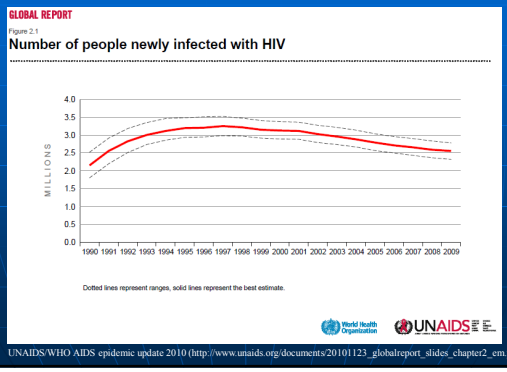
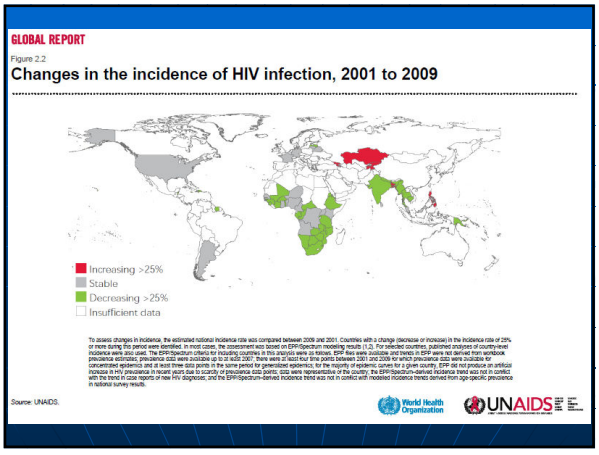
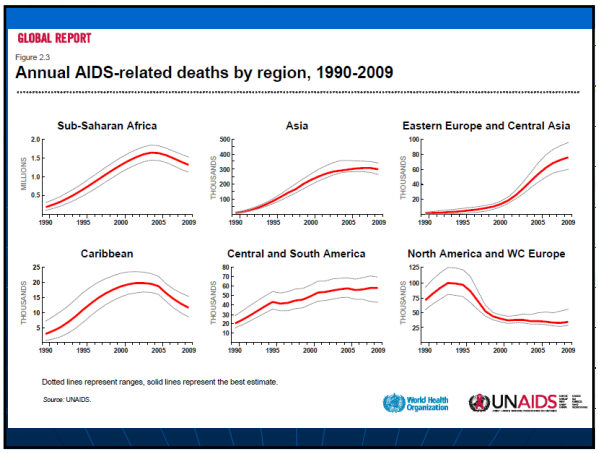
HIV in the World



UNAIDS/WHO AIDS epidemic update 2010 (http://www.unaids.org/documents/20101123_globalreport_slides_chapter2_em.pdf)





HIV/TB in the World

- Estimated 9.4 million new TB cases in 2009
  - About 1.1 million coinfected with HIV
- Estimated 1.7 million TB deaths in 2009
  - 380,000 HIV-coinfected
- TB incidence stable or falling in all 6 WHO regions

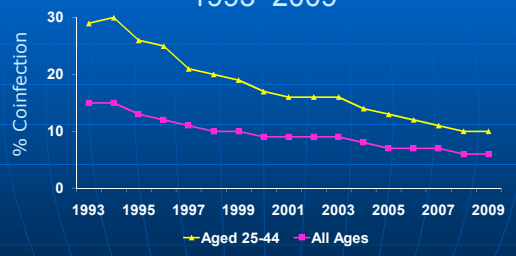
http://www.who.int/tb/publications/global_report/2010/gtbr10_main.pdf/

HIV in the US

- At the end of 2003, an estimated 1,039,000 to 1,185,000 persons in the US were living with HIV/AIDS
- 24-27% did not know they had HIV

Glynn M, Rhodes P. Estimated HIV prevalence in the United States at the end of 2003. National HIV Prevention Conference; June 2005; Atlanta. Abstract 595.

Estimated HIV Coinfection in Persons Reported with TB, United States, 1993–2009*



*Updated as of July 1, 2010.

Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.

Effect of HIV on TB

- Increased risk of progression to disease once infected:
  - HIV-: 10% lifetime risk of TB disease
  - HIV+: 10% YEARLY risk of TB disease
- Even early HIV infection significantly increases vulnerability
  - Doubling of TB incidence in S. African miners in 1st year after HIV infection

Sonnenberg P et al., *J Infect Dis* 191: 150 2005

Effect of HIV on TB

- Altered disease presentation
  - More extrapulmonary disease
  - More disseminated disease
  - More smear-negative disease
- Harder to detect
  - Cavities less common
  - 5-10% of HIV+ with pulm TB can have normal CXR!

Effect of TB on HIV

- Increased HIV replication
- Possibly increased long-term mortality
  - Study of HIV/TB pts published in mid-90s described 10% mortality/yr for HIV+ persons without TB
  - Increased to 35%/yr in HIV/TB even after successful TB treatment
  - May not be true in HAART era

Issues with TB/HIV treatment

- Recent study of 367 HIV/TB pts diganosed 1987-2000 highlights issues
- 15.5% required TB drug change due to intolerance
- 38.2% had poor adherence to TB rx
- 24.5% had liver disease before or during rx

Dworkin MS, Adams MR, Cohn DL, et al. Factors that complicate the treatment of tuberculosis in HIV-infected patients. J Acquir Immune Defic Syndr. 2005; 39(4):464-70.

Issues with TB/HIV treatment

- 72.6% were concurrently taking rifamycins and HIV drugs that interact with rifamycins
- 61.6% completed TB treatment
- 16.6% died within 12 months of TB diagnosis

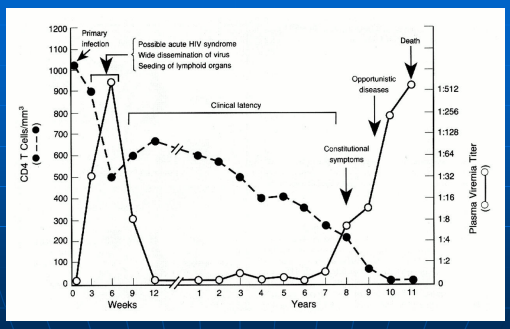
TB vs. HIV therapy

TB	HIV
Multiple drugs required to treat	Multiple drugs required to treat
Long course of therapy	Indefinite course of therapy
Drug intolerance common	Drug intolerance common
Curable	Not curable (yet!)

Basics of HIV

- Virus infects CD4+ lymphocytes, some other cell types
- Infection usually occurs via sex, blood contact, mother-child
- Many persons symptomatic at time of acute infection (mono-like illness)
- Variable asymptomatic period thereafter

Typical Course of HIV Infection



Pantaleo, G. et al. N Engl J Med 1993;328:327-335

The NEW ENGLAND JOURNAL of MEDICINE

HIV treatment

- Initiated when CD4<200 (<350) or in setting of symptomatic disease
- 5 classes of drugs:
  - NRTIs
  - NNRTIs
  - PIs
  - Integrase inhibitors
  - Fusion/entry inhibitors
- Regimens usually include at least 3 drugs from 2 different classes

NRTIs

- Zidovudine (AZT)
- Lamivudine (3TC)
- Stavudine (d4T)
- Emtricitabine (FTC)
- Didanosine (ddI)
- Abacavir (ABC)
- Tenovovir (TFV)
- ~~Zalcitabine (ddC)~~
- Combivir®=AZT +3TC
- Truvada®=FTC + TFV
- Epzicom®=ABC + 3TC
- Trizivir®=AZT + 3TC + ABC

NNRTIs

- Efavirenz (Sustiva®)
- Nevirapine (Viramune®)
- ~~Delaviradine (Rescriptor®)~~
- Etravirine (Intelence®)
- Rilpivirine (Edurant®)
  - (approved 5/20/11)

Protease Inhibitors

- Darunavir (Prezista®)
- Lopinavir/ritonavir (Kaletra®)
- Atazanavir (Reyataz®)
- Fosamprenavir (Lexiva®)
- Indinavir (Crixivan®)
- Saquinavir (Invirase®)
- Tipranavir (Aptivus®)
- Nelfinavir (Viracept®)
- Ritonavir (Norvir®)

Integrase Inhibitors

- Raltegravir (Isentress®)

Fusion/Entry Inhibitors

- Enfuvirtide (Fuzeon®)
- Maraviroc (Selzentry®)

HIV Treatment

- Older regimens often included many pills taken bid-tid
- New regimens as simple as 1 pill daily
- Goal is to achieve plasma HIV RNA (viral load) below limits of detection
- Up to 90% of previously untreated patients can do this with modern regimens

Drug Interactions

- Rifamycins (rifampin, rifabutin, rifapentine) induce P450 enzymes
- Result is lower blood concentrations of drugs metabolized by those enzymes
- Metabolic changes can be dramatic, resulting in ineffective therapy

Drug Interactions

- Ritonavir inhibits P450 enzymes
- Result is increased concentrations of target drugs (e.g. rifabutin)
- Efavirenz induces P450 enzymes
- Result is decreased concentrations of target drugs (e.g. rifabutin)

RIFAMPIN, RIFAPENTINE

PI

NNRTI

Rifabutin

Drug interactions-rules of thumb

- NRTIs and enfuvirtide don't interact with TB drugs in a clinically significant way
- PIs, IIs and NNRTIs are chewed up by rifamycins (decreased exposure)
- Rifabutin is chewed up by efavirenz, boosted by PIs
- Rifampin is unaffected by other drugs

Effect of protease inhibitors on serum concentrations (AUC) of rifamycins

PI	Rifabutin	Rifampin
Saquinavir	↑ 45%	NR
Ritonavir	↑ 400%	unchanged
Indinavir	↑ 270%	unchanged
Nelfinavir	↑ 200%	NR
Amprenavir	↑ 400%	NR
Lopinavir/ritonavir	↑ 300%	NR
Atazanavir	↑ 250%	NR

Clin Infect Dis 1999; 28: 419-30

Recommended antiretroviral regimens with rifampin or rifabutin

Rifampin	Rifabutin
▪ Efavirenz (consider dose of 800 mg)	▪ Protease inhibitors (usually need to ↓ RBT dose) ▪ Efavirenz (↑ RBT dose to 600 mg) ▪ Nevirapine

Rifabutin (Mycobutin®)

- Susceptibility/resistance same as rifampin
- Less induction of liver metabolism
  - recommended to replace rifampin if significant drug interaction likely
  - e.g., HIV medications, cyclosporine
- Dose 300 mg qD, but must be adjusted for certain co-administered medications

Rifabutin (Mycobutin®)

- More expensive
- Less clinical experience
- Side effects
  - GI, rash
  - uveitis

Use of Rifabutin

- Rifabutin can be safely used with most protease inhibitors and NNRTIs, except saquinavir and delavirdine
- Unlike rifampin and rifapentine, however, dosage of rifabutin must be altered since other ARV drugs affects its serum concentration

Drug Interactions

- Bottom line: Look it up!
- Most up-to-date recs:
  - http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm
  - NC TB Manual: http://www.epi.state.nc.us/epi/gcdc/tb/manual.html

Is it worth the hassle?

TABLE 5. COMPARISON OF USE OF COMBINATION ANTIRETROVIRAL THERAPY AND RATES OF HIV DISEASE PROGRESSION IN A TREATMENT OF HIV-RELATED TUBERCULOSIS IN THE UNITED STATES AND CANADA IN THE ERA PRIOR TO POTENT ANTIRETROVIRAL THERAPY VERSUS THE PRESENT STUDY

	CPCRA/ACTC* (*n* = 101)	Present Study (*n* = 169)
Years of enrollment	1993–1995	1999–2002
Median enrollment CD4 cell count (IQR)	86 (35–230)	90 (35–175)
Use of potent antiretroviral therapy during TB treatment, n (%)	0	137 (81)
Death within 12 mo of starting TB treatment (% by Kaplan-Meier analysis)	20.0	4.9
HIV disease progression (new opportunistic infection or death) within 12 mo of starting TB treatment (% by Kaplan-Meier analysis)	38.9	15.4

Definition of abbreviations: ACTG = AIDS Clinical Trials Group; CPCRA = Community Programs for Clinical Research on AIDS; IQR = interquartile range; TB = tuberculosis.
* Data from Reference 5.

Burman W et al., *AJRCCM* 173:350 2005

Treatment of HIV in TB/HIV Pts

- Increased pill burden
- Complex drug interactions
- Immune Reconstitution Inflammatory Syndrome (IRIS)

What Actually Happens?

- Difficult populations to treat
- Poor access/utilization of HIV specific healthcare
- Suboptimal outcomes

TB/HIV in NC 93-03

- Cohort study of 543 cases of TB/HIV reported in NC 1993-2003 (inclusive)
- Looked at TB treatment outcomes, HIV healthcare utilization, mortality
- Data obtained from registry, HD charts

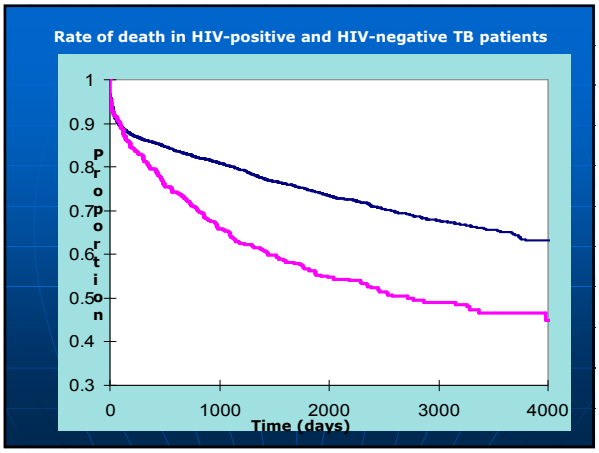
Gadkowski LB et al, *AIDS Pt Care STDs* 2009; 23: 845-851

Opportunistic Infections

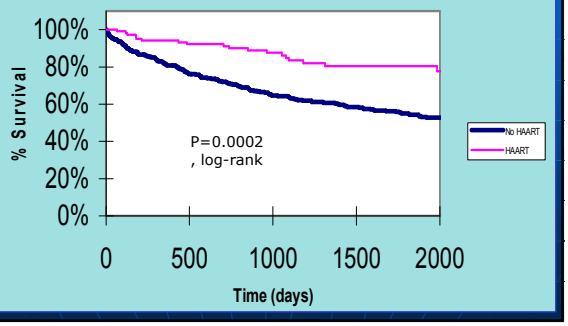
- 54/433 (12.5%) of subjects with chart data available had a history of an OI prior to TB presentation
- 79 (18.2%) were diagnosed with an OI concurrently with TB diagnosis
- 55 (12.7%) had a new OI during TB treatment

Opportunistic Infections

OI	Prior to rx	On Presentation	During rx
PCP	23	8	9
Thrush	33	65	37
Esophageal candidiasis	8	11	10
CMV	2	4	0
Crypto	1	1	4
PML	0	0	0
Toxo	1	3	5
MAC	6	4	5



Survival after TB Diagnosis Among TB/HIV Coinfected Persons Depending on Whether HAART Was Started During TB Treatment



Death During TB Treatment (Multivariable Analysis)

Factor	Relative Risk (95% CI)
Age >45	2.03 (1.03-4.01)
Baseline CD4 (per 100 cells/mm^3)	0.53 (0.34-0.82)
HAART started during TB treatment	0.38 (0.14-1.06)

TB is an Opportunity for HIV Care

- Opportunity for HIV testing (all should be tested)
- Opportunity for HIV treatment
- Opportunity to optimize adherence to HIV treatment

Effectiveness of TB rx in HIV+

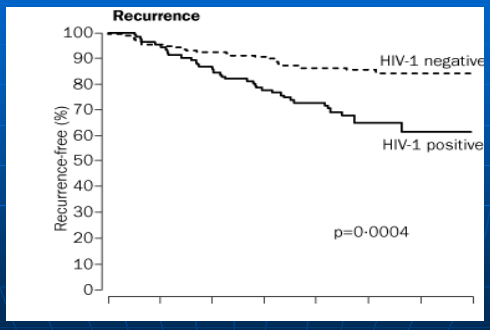
- Physicians have tended to treat HIV+ patients for longer
- Official guidelines state 6 mos of rx for HIV+ or – pulmonary disease
- What is the evidence?

Comparison of outcomes by HIV serostatus in studies of 6-month regimens given as DOT

Study (n)	HIV positive		HIV negative	
	Treatment failure (%)	Recurrence (%)	Treatment failure (%)	Recurrence (%)
Haiti (427)	2.0	5.4	3.0	2.8
South Africa (403)	3.0	5.0	7.0	5.0
Baltimore (280)	0	6.0	0	3.0
South Africa (385)	5.3	21.5	8.1	13.0

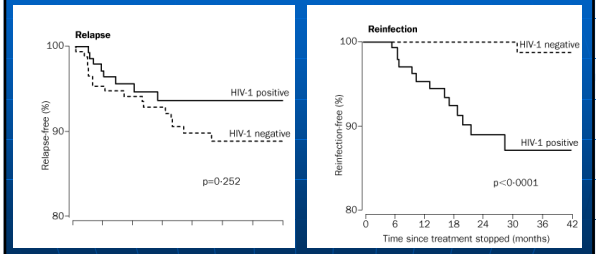
All included rifampin and PZA in regimen

Comparison of recurrence rates by HIV serostatus



Lancet 2001;358:1687-93

Relapse vs. re-infection by HIV-serostatus



Lancet 2001;358:1687-93

Risk factors for TB treatment failure or relapse in recent studies of HIV-related TB

- CPCRA/ACTG study - low CD4 cell count
- TBTC Study 22 - low CD4 cell count, extrapulmonary involvement, azole use, younger age
- TBTC Study 23 - low CD4 cell count
- Baltimore cohort - low CD4 cell count

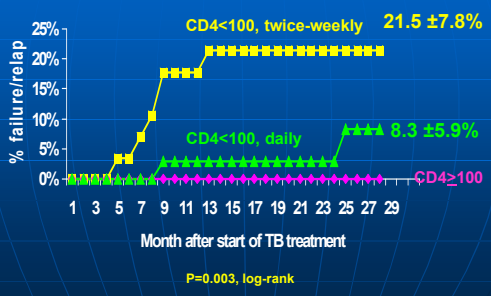
Acquired Drug Resistance

- INH and SM resistance patterns common
- Rifampin resistance very unusual unless part of multi-drug resistance pattern
- Rifampin mono-resistance has been strongly associated with those with HIV/AIDS and TB

Acquired Drug Resistance

- CDC and TB Trials Consortium Study 23
- Substituted rifabutin for rifampin
- 9/169 (5.3%) failed/relapsed
- 8/9 acquired RIF-resistant disease
  - All with CD4 < 60

Study 23: Time to acquired rifamycin-resistant treatment failure or relapse



P=0.003, log-rank

Acquired Drug Resistance

- Two consistent risk factors for acquired resistance:
  1) low CD4 cell count (<100)
  2) treatment with once- or twice-weekly therapy
- No apparent difference between rifabutin and rifampin

Acquired Drug Resistance

- Likely occurs because of malabsorption
- Lower AUC of INH+/- rifamycin have been associated with acquired rifamycin resistance
- Unclear how much absorption is required to prevent this problem

How does this change rx?

- For patients with CD4 < 100
  - Give daily therapy throughout the course
  - All DOT except weekends
- If apparent treatment failure, assume RIF mono-resistance has developed

Case Study

- Patient X, CD4 recently dropped to 56, dx lymph node TB
- Need to start TB treatment
  - Daily or intermittent?
  - Daily because CD4 <100
- Initial TB therapy standard, with rifampin

Case Study

- Physician & patient want to re-start ARV
  - Need ritonavir-boosted protease-inhibitor regimen
    - Why?
    - Problem?
- Stop rifampin, start rifabutin
  - What dose of rifabutin?
  - When to start ARV?

Case Study

- Daily INH and 300 mg daily rifabutin
- After 2 weeks (allowing rifampin effects to wash-out), start ritonavir-boosted PI regimen
  - And do what with the rifabutin?
  - Change to 150 mg qod
  - Why? I thought we needed daily therapy?

Case Study

- Rifabutin 150 mg qod in the setting of ritonavir (which is blocking the metabolic pathway) EQUATES to daily RBT 300 mg
- IF patient become non-compliant with the boosted PI regimen – what happens to the RBT levels?
  - Too low

Management Summary: TB and HIV/AIDS

- Find out CD4 count
  - part of standard of care for HIV/AIDS
- If CD4 >100, usual TB therapy
  - daily 14 days then twice or 3 times weekly DOT
- If CD4 <100, DAILY DOT 6 months
  - self-meds on weekends

Management Summary: TB and HIV/AIDS

- If NOT on antiretroviral therapy
  - treatment & follow-up is the same
    - must document sputum culture conversion
    - if evidence of failure or relapse, assume rifampin monoresistance until proven otherwise

Management Summary: TB and HIV/AIDS

- Refer patient to HIV/AIDS specialist
- Always look at the patients medication list
- Always discuss plan for care with both the TB doctor and the patient's HIV doctor
- Recognize that you may be the "expert"

Management Summary: TB and HIV/AIDS

- Plan to treat for minimum of 4 months after culture conversion
- As with non-HIV
  - cavity on chest x-ray initially and
  - culture + at 2 months
  - plan on minimum of 9 months therapy

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Analogous to paradoxical reactions seen in pts with advanced TB
- Occur in 18-36% of pts with TB/HIV
- Usual setting is pt with low CD4 count, started on ARV with good suppression of viral load and rapid rise in CD4

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Recent review identified 86 published cases of IRIS in pts with HIV/TB
- Median CD4 nadir=51
- Risk factors:
  - Extrapulmonary TB
  - Starting HIV rx prior to completion of 2 months of TB rx

Lawn SD et al, *Lancet Inf Dis* 5:361 2005

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Usually occurs 2-10 weeks after starting HIV rx
- Common symptoms:
  - Fever
  - Increasing or new lymphadenopathy (>70% of cases)
  - Worsening respiratory symptoms
- HIV rx interrupted 15% of the time
- 7% required surgery!

IRIS events during TBTC Study 23

- 26 patients had 30 events; 2 events were related to an infection other than TB (1 – coccidioidomycosis, 1-HPV)
- Analysis includes the 25 initial IRIS events related to TB
- All events among 137 patients who received antiretroviral therapy – 25/137 = 18%

IDSA 2004, poster 904

IRIS manifestations in HIV-related TB

- Hectic fever
- New or worsening adenitis - peripheral or central nodes
- New or worsening pulmonary infiltrates, including respiratory failure
- New or worsening pleuritis, pericarditis, or ascites
- Intracranial tuberculomas, worsening meningitis
- Disseminated skin lesions
- Epididymitis, hepatosplenomegaly, soft tissue abscesses

IRIS Considerations

- Those who need HIV rx the most (patients with low CD4 cell counts) are at the highest risk for IRIS
- Delaying HIV rx may decrease risk of severe paradoxical reactions, but may increase risk of another OI or death
- Anticipate paradoxical reactions – discuss beforehand with patient and other care providers
- Schedule early follow-up after starting ARV - detect and manage paradoxical reactions

IRIS Management

- No data to support any specific strategies
- Corticosteroids and/or NSAIDs are frequently used
- Repeated aspiration of superficial lymph nodes may be useful
- ? Thalidomide or other immunomodulators

Summary

- Improved life expectancy for HIV+
- HIV-TB co-infection is fueling massive world outbreak of TB
- Treatment of TB in the setting of HIV will likely be successful, but
- Requires consultation with experts

Where to find HELP!

- State TB Medical Team
  - Dr. Jason Stout
  - Dr. David Holland
- Local and academically-based ID experts